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Cardiovascular clusters in septic shock combining clinical and echocardiographic parameters: a post hoc analysis

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Abstract

Purpose: Mechanisms of circulatory failure are complex and frequently intricate in septic shock. Better characterization could help to optimize hemodynamic support.

Methods: Two published prospective databases from 12 different ICUs including echocardiographic monitoring performed by a transesophageal route at the initial phase of septic shock were merged for post hoc analysis. Hierarchical clustering in a principal components approach was used to define cardiovascular phenotypes using clinical and echocardiographic parameters. Missing data were imputed.

Findings: A total of 360 patients (median age 64 [55; 74]) were included in the analysis. Five different clusters were defined: patients well resuscitated (cluster 1, $n=61$, 16.9%) without left ventricular (LV) systolic dysfunction, right ventricular (RV) failure or fluid responsiveness, patients with LV systolic dysfunction (cluster 2, $n=64$, 17.7%), patients with hyperkinetic profile (cluster 3, $n=84$, 23.3%), patients with RV failure (cluster 4, $n=81$, 22.5%) and patients with persistent hypovolemia (cluster 5, $n=70$, 19.4%). Day 7 mortality was 9.8%, 32.8%, 8.3%, 27.2%, and 23.2%, while ICU mortality was 21.3%, 50.0%, 23.8%, 42.0%, and 38.6% in clusters 1, 2, 3, 4, and 5, respectively ($p<0.001$ for both).

Conclusion: Our clustering approach on a large population of septic shock patients, based on clinical and echocardiographic parameters, was able to characterize five different cardiovascular phenotypes. How this could help physicians to optimize hemodynamic support should be evaluated in the future.

Keywords: Septic shock, Hemodynamic failure, Cluster

Introduction

In the past, it was considered that hemodynamic alterations in septic shock occur in different phases, an early phase with a low flow state related to hypovolemia, a second phase after the initial resuscitation with a hyperdynamic state, and finally a third phase with cardiac failure leading to multiorgan failure and death [1]. Since the landmark study by Parker et al. [2], it has been progressively accepted that depressed left ventricular (LV) systolic function may develop at the early phase of septic shock. For a long time, the assessment of hemodynamic instability in septic shock was based on right heart catheterization, while alternatives are now well recognized, including critical care echocardiography (CCE) [3]. The high incidence of early myocardial alterations has been confirmed by echocardiographic studies [4, 5] and one found an incidence of LV systolic dysfunction of 39% during the first day [6]. There is then an urgent need for better characterization of cardiovascular phenotypes

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in order to propose targeted/personalized medicine for hemodynamic support [7], as for the adequate need for fluids [8, 9] or inotropic support. Although CCE may detect combined mechanisms of circulatory failure in septic shock (i.e., vasoplegia, hypovolemia, LV systolic dysfunction, and right ventricular (RV) failure) [10], it failed to extend such an integrative and individualized approach in daily clinical practice. Cardiovascular phenotypes are insufficiently characterized and rely on too simplistic and inadequate definitions, as reflected by the binary approach mostly based on the value of LV ejection fraction (EF) to identify sepsis-induced LV systolic dysfunction [11].

We therefore hypothesized that the application of a clustering approach to a large database of septic shock patients monitored by CCE could help to better characterize the different cardiovascular phenotypes.

Take-home message

Using a clustering approach including clinical and echocardiographic parameters, 5 different hemodynamic phenotypes were identified in 360 septic shock patients, left ventricular (LV) systolic dysfunction, LV hyperkinesia, still hypovolemia, right ventricular failure and well-resuscitated phenotype.

Materials and methods

Study design

The databases of two recently published prospective, observational, multicenter studies using CCE during early resuscitation of patients with septic shock were merged. The Hemosepsis study (inclusion January 2011–December 2013) compared the identification of hemodynamic profiles using both CCE and transpulmonary thermodilution in septic shock patients in sinus rhythm [12]. The Hemopred study included patients (November 2012–November 2014) with shock of any origin, mostly related to sepsis, to compare the accuracy of the different parameters of fluid responsiveness [13]. In both cohorts, we excluded patients with a history of chronic heart failure. Overall, the patients included came from 12 different ICUs. Septic shock was not defined by the Sepsis-3 definition as Hemopred and Hemosepsis were designed before its publication. Diagnosis was based on a suspected infection responsible for sustained hypotension despite adequate fluid loading that required vasopressors, with associated clinical signs of tissue hypoperfusion (mottled skin, encephalopathy, oliguria for more than 2 h) that were biologically confirmed (pH < 7.38 and base deficit > − 5 mmol/L or lactate > 2 mmol/L or central venous oxygen saturation < 70%).

CCE

CCE was performed using a transesophageal route (TEE) in all patients during the first 12 h following the diagnosis of septic shock, after initial fluid resuscitation and vasopressor infusion. Patients were all intubated, sedated, and perfectly adapted to the respirator, as no spontaneous effort was observed during the echo procedure. Views, recorded parameters, and measurements were extensively described previously following the same prospective procedure [12, 13]. Echo parameters are all well recognized in the literature as good/adequate parameters of cardiovascular status in sepsis. Briefly, we systematically measured parameters of LV systolic function, i.e., LVEF and LV fractional area change (FAC) [14], and of LV diastolic function, i.e., maximal mitral Doppler *E* wave velocity and maximal tissue Doppler velocity of the lateral aspect of the mitral annulus at early diastole (*E*′) [15]. RV function was evaluated by the RV/LV end-diastolic area (EDA) ratio [16]. Fluid responsiveness was assessed using the superior vena cava collapsibility index (ΔSVC) [17]. We measured the velocity time integral (VTI) in the LV outflow tract and the diameter of the aortic annulus, which allowed us to calculate LV stroke volume and cardiac index (CI) [18]. The ultrasound systems used in the two cohorts were the same in each participating center as a result of the relatively narrow period of time encompassing the two studies. Images were all obtained and interpreted by intensivists trained in advanced level CCE, as mentioned in the two original studies. Images were not "validated" by independent experts to increase the external validity of our results which correspond to hemodynamic data obtained during daily echocardiographic assessment on clinical grounds. Importantly, no a priori criteria of "abnormality" were applied for the different parameters to best take into account inter-individual variabilities, allowing better characterization of cardiovascular phenotypes.

Patient characteristics and clinical hemodynamic evaluation

We calculated the sequential organ failure assessment (SOFA) score and the simplified acute physiology score (SAPS II). Mortality at day 7 and in the ICU was also recorded, as was the origin of infection.

In each patient, several clinical hemodynamic parameters were prospectively recorded at the time of the CCE: heart rate, invasive systolic (SAP), diastolic (DAP), and mean arterial pressure (MAP); central venous pressure (CVP) and central venous oxygen saturation ($ScVO_2$) were measured through a catheter placed in the internal jugular or subclavian vein; serum lactate level, volume of initial filling, presence of epinephrine, dobutamine, or norepinephrine and if so respective doses were also

recorded. We also recorded blood gas analysis and respiratory settings.

Statistical analysis

Baseline characteristics were reported as median [interquartile range] and *n* (%) for quantitative and qualitative variables, respectively. Quantitative variables were compared using nonparametric tests, the Mann–Whitney test or the Kruskal–Wallis test, as appropriate. Qualitative variables were compared using Pearson's Chi-square test or Fisher's exact test, as appropriate.

A two-step clustering approach was used to (1) reduce the dimensionality of the dataset and (2) to perform hierarchical clustering. This approach, so-called hierarchical clustering on principal components (HCPC), was performed using the factoMineR package in R [19]. We first performed a principal component analysis including hemodynamic parameters (i.e., LVEF, LVFAC, mitral Doppler *E* wave velocity, lateral mitral tissue Doppler *E*′ velocity, aortic VTI, RV/LV EDA, ΔSVC, systolic arterial blood pressure, diastolic arterial blood pressure, heart rate, norepinephrine and epinephrine infusion doses). Variables were standardized as they were measured in different units. The HCPC procedure allows one, after the hierarchical clustering step is performed, to choose the number of clusters based on the hierarchical tree and to perform a K-means clustering to improve the initial partition obtained from the hierarchical clustering [20]. Agglomerative hierarchical clustering used the Ward's criterion and an Euclidean metric. Data on the internal validity and stability of the analysis are shown in the supplementary material (Fig. S1). Missing data were imputed using iterative principal component analysis (implemented in the imputePCA R function), as previously described. Briefly, this method starts using a mean imputation, performs principal component analysis on the completed dataset, and missing values are then updated by the fitted values using a predefined number of dimensions [21]. Multiple imputations were also performed to visualize the variability related to the imputation process (Fig. S2).

We then compared variables (hemodynamic and non-hemodynamic-related variables) according to clusters. We chose not to include hemodynamic variables whose proportion of missing values was higher than 10%.

Last, we evaluated the diagnostic performance of the three most important variables for each cluster using two methods: (1) evaluation of the area under the receiver operating curve (AUROC) of a multivariable logistic regression with a binary variable of being in each cluster (yes/no) as the dependent variable and these three variables as independent variables and (2) calculation of sensitivity, specificity, and negative and positive predictive values for the combination of these three variables above or below the thresholds. These thresholds were picked up from the description of the hemodynamic parameters we described across clusters as follows: the first interquartile (Q1) when the mean of the cluster was lower than the overall mean and the third interquartile (Q3) when the mean of the cluster was higher than the overall mean; 95% confidence intervals were calculated for all these results.

A p value lower than 0.05 was considered significant. All statistical analyses were performed using RStudio (Version 1.1.414—2009–2018 RStudio, Inc.).

Role of the funding source

The Hemosepsis study was financially supported by the Programme de Recherche Clinique Inter-régional (academic financial support provided by the French Ministry of Health). The Hemopred study was financially supported by the CIC-P 1435, CHU Limoges. Neither sponsor was involved in any step of the present work.

Results

Among 432 patients from both cohorts, 360 were analyzed (Fig. S3). We excluded from the analysis 50 patients with a history of chronic heart failure, as it was not at all characterized. In most patients (82%), there was no missing data (Fig. S4). Characteristics of the population and mortality are reported in Table 1. Median age was 64 [interquartile 55; 74], SOFA score 10 [7; 12], and SAPS II 57 [45; 70]. No difference was observed between patients initially included in the Hemosepsis or Hemopred cohort regarding severity scores (Table S1). Twenty-one patients (5.8%) were in atrial fibrillation at the time of CCE and 42 patients (11.7%) already received inotropic drug (dobutamine, $n=17$ or epinephrine, $n=25$). Day 7 and in-ICU mortality were 20.1% and 35%, respectively.

Analysis in clusters characterized five distinct cardiovascular phenotypes (Tables 1, 2; Fig. 1). Sixty-one patients (16.9%) could be considered as "well resuscitated" (cluster 1), since we observed neither LV systolic dysfunction and RV failure nor fluid responsiveness. Both CI and $ScvO_2$ were within the normal range. Sixty-four patients (17.7%) had an "LV systolic dysfunction" phenotype (cluster 2). These patients exhibited low LVEF, LVFAC, and CI (29% [22; 40], 26% [18; 33], and 2.2 L/min/m^2 [1.7; 2.5], respectively), had higher lactate level, required a higher dose of norepinephrine, and were not fluid responders. Only nine of these patients had a LVEF higher than 45%. $ScVO_2$ remained within the normal range. Similarly, LV filling pressure as reflected by E/E' ratio remained non-elevated despite cardiac failure. Eighty-four patients (23.3%) had a phenotype reflecting a

Table 1 Baseline characteristics of the patients included in the analysis according to cluster partition

	All patients	Cluster					*p* value
		1	2	3	4	5	
	N = 360	*n* = 61	*n* = 64	*n* = 84	*n* = 81	*n* = 70	
Demographics							
Age, years	64 [55; 74]	59.0 [50.0; 68.0]	64.0 [54.0; 75.0]	66.0 [59.0; 75.0]	63.0 [55.0; 73.0]	64.0 [55.0; 76.0]	0.011
Male gender	233 (64.7)	35 (57.4)	40 (62.5)	62 (73.8)	54 (66.7)	42 (60.0)	0.245
Chronic respiratory failure	52 (14.4)	5 (1.4)	12 (3.3)	12 (3.3)	12 (3.3)	11 (3.1)	0.561
Atrial fibrillation at time of CCE	21 (5.8)	4 (1.1)	6 (1.7)	4 (1.1)	3 (0.8)	4 (1.1)	0.670**
SAPS II	57 [45; 70]	50.0 [39.0; 63.0]	62.0 [51.0; 74.0]	55.0 [42.0; 67.0]	59.5 [48.0; 72.0]	56.5 [44.0; 70.0]	0.004
SOFA score	10 [7, 12]	10.0 [8.0; 12.0]	10.0 [8.0; 12.5]	10.0 [7.0; 11.0]	11.0 [7.5; 13.0]	9.0 [7.0; 11.0]	0.089
Arterial blood lactate level, mmol/L	2.5 [1.5; 4.3]	2.7 [1.6; 4.1]	3.1 [2.1; 6.6]	1.9 [1.3; 3.0]	2.6 [1.6; 4.0]	2.7 [1.6; 4.7]	< 0.001
Non-hemodynamic parameters							
$PaCO_2$, mmHg	40 [34; 47]	42.0 [35.9; 49.0]	40.0 [33.5; 44.5]	40.3 [35.0; 48.0]	40.0 [33.5; 47.3]	38.5 [34.0; 43.0]	0.376
PaO_2/FiO_2, mmHg	184 [113; 262]	170.5 [111.9; 258.8]	174.0 [92.9; 241.8]	195.5 [120.3; 269.4]	153.8 [105.5; 231.5]	204.0 [125.0; 296.0]	0.099
PaO_2/FiO_2 ratio Berlin classification*							0.628
> 300 mmHg, *n* (%)	57 (15.9)	12 (20.0)	8 (12.5)	13 (15.5)	9 (11.2)	15 (21.4)	
200–300 mmHg, *n* (%)	100 (27.9)	14 (23.3)	20 (31.2)	26 (31.0)	20 (25.0)	20 (28.6)	
< 200 mmHg, *n* (%)	201 (56.1)	34 (56.7)	36 (56.2)	45 (53.6)	51 (63.8)	35 (50.0)	
Site of infection							0.001
Lung, *n* (%)	169 (46.9)	22 (36.1)	23 (35.9)	43 (51.2)	48 (59.3)	33 (47.1)	
Urinary tract, *n* (%)	25 (6.9)	3 (4.9)	7 (10.9)	7 (8.3)	4 (4.9)	4 (5.7)	
GI tract, *n* (%)	109 (30.3)	20 (32.8)	26 (40.6)	21 (25.0)	13 (16.0)	29 (41.4)	
Skin, *n* (%)	24 (6.7)	8 (13.1)	4 (6.2)	7 (8.3)	2 (2.5)	3 (4.3)	
Others, *n* (%)	33 (9.2)	8 (13.1)	4 (6.2)	6 (7.1)	14 (17.3)	1 (1.4)	
Outcome							
Day 7 mortality, *n* (%)	72 (20.1)	6 (9.8)	21 (32.8)	7 (8.3)	22 (27.2)	16 (23.2)	< 0.001
ICU mortality, *n* (%)	126 (35.0)	13 (21.3)	32 (50.0)	20 (23.8)	34 (42.0)	27 (38.6)	0.001

*Two missing FiO_2

**Exact Fisher's test

"hyperkinetic" state (cluster 3). In these patients, LV systolic function (LVEF 60% [52.5; 66]) and CI (3.3 L/min/m^2 [2.3; 4.3]) were increased compared to other clusters, and patients exhibited no sign of fluid responsiveness. Eighty-one patients (22.5%) had a hemodynamic profile consistent with underlying "RV failure" (cluster 4). These patients exhibited a markedly high RV/LV EDA ratio (0.8 [0.6; 0.9]) with a normal or supranormal LV systolic function (LVEF 57% [46; 64]) and no more fluid responsiveness. In this subset of patients, more patients had a PaO_2/FiO_2 lower than 200 mmHg. Finally, 70 patients (19.4%) belonged to the last cardiovascular phenotype which could be named "still hypovolemic" (cluster 5). These patients exhibited a low CI (2.6 L/min/m^2 [1.9; 3.1]) despite an increased LV systolic function (LVEF 58% [50; 65]) due to sustained fluid responsiveness, as reflected by markedly elevated ΔSVC (39% [31; 54]), and low preload (CVP 8 mmHg [5; 12]). Interestingly, patients in this cluster received significantly more fluids before CCE than the others, 2762 mL [2500; 4000] and 2000 mL [1000; 3433],

Table 2 Hemodynamic data of the 360 patients included in the study according to the cluster partition

	All patients	Cluster					*p* value
		1	2	3	4	5	
	N = 360	*n* = 61	*n* = 64	*n* = 84	*n* = 81	*n* = 70	
Hemodynamic parameters							
Heart rate, per minute	107 [90; 124]	125.0 [115.0; 140.0]	111.0 [98.0; 127.5]	93.0 [79.5; 106.0]	103.0 [85.0; 116.0]	111.0 [99.0; 125.0]	< 0.001
Systolic arterial blood pressure, mmHg	112 [96; 129]	129.0 [115.0; 141.0]	111.5 [101.5; 124.0]	127.0 [114.0; 139.0]	90.0 [80.0; 100.0]	105.0 [95.0; 120.0]	< 0.001
Diastolic arterial blood pressure, mmHg	59 [51; 70]	67.0 [58.0; 76.0]	70.0 [59.5; 76.0]	63.0 [54.0; 70.5]	47.0 [40.0; 51.0]	59.0 [53.0; 68.0]	< 0.001
Mean arterial blood pressure, mmHg	77 [67; 88]	84.0 [77.0; 97.0]	81.5 [72.5; 92.0]	84.5 [75.0; 91.0]	61.0 [52.0; 67.0]	74.0 [68.0; 82.0]	< 0.001
Cardiac index, L/min/m^2	2.9 [2.1; 3.8]	3.8 [3.0; 4.4]	2.2 [1.7; 2.5]	3.3 [2.3; 4.3]	3.2 [2.4; 3.9]	2.6 [1.9; 3.1]	< 0.001
$ScvO_2$, %	79 [71; 85]	80.0 [72.1; 86.2]	78.0 [66.0; 84.1]	82.3 [75.0; 85.0]	77.7 [69.1; 84.0]	77.0 [69.4; 84.0]	0.038
Central venous pressure, mmHg	10 [7, 13]	11.0 [8.0; 13.5]	10.0 [9.0; 14.0]	10.0 [7.5; 12.0]	9.0 [6.0; 13.0]	8.5 [5.5; 12.0]	0.041
Fluid expansion before CCE, mL	2000 [1000; 3500]	2000 [1228; 3433]	2000 [1000; 3500]	2000 [1500; 3000]	2000 [1000; 3289]	2762 [2500; 4000]	0.175
Hemodynamic treatments							
Epinephrine infusion, *n* (%)	25 (6.9)	7 (11.5)	11 (17.2)	6 (7.1)	0 (0.0)	1 (1.4)	< 0.001
Epinephrine infusion rate, mg/h	0.0 [0.0; 0.0]	0.0 [0.0; 1.0]	0.0 [0.0; 0.0]	0.0 [0.0; 0.0]	0.0 [0.0; 0.0]	0.0 [0.0; 0.0]	< 0.001
Norepinephrine infusion, *n* (%)	309 (85.8)	58 (95.1)	56 (87.5)	64 (76.2)	70 (86.4)	61 (87.1)	0.027
Norepinephrine infusion rate, mg/h	1.9 [0.6; 4.0]	2.2 [1.0; 4.0]	3.0 [1.5; 5.5]	1.0 [0.2; 2.3]	2.1 [0.7; 5.0]	1.8 [0.8; 3.5]	< 0.001
Dobutamine infusion, *n* (%)	17 (4.7)	1 (0.3)	6 (1.7)	2 (0.6)	5 (1.4)	3 (0.8)	0.246*
Dobutamine infusion rate, µg/kg/min	5 [5; 7.5]	5**	5 [5; 6.9]	6 [5.5; 6.5]	8 [5; 10]	5 [3.7; 5,5]	0.551
Echocardiographic parameters							
LVEF, %	54 [40; 64]	51.0 [40.0; 60.0]	29.5 [22.0; 40.5]	60.0 [52.5; 66.0]	57.0 [46.0; 64.0]	57.9 [50.0; 65.0]	< 0.001
LVFAC, %	46 [33; 58]	39.0 [29.0; 47.0]	26.0 [18.5; 33.4]	58.0 [46.9; 64.6]	53.0 [42.0; 63.0]	50.0 [43.0; 60.0]	< 0.001
Mitral *E* wave, cm/s	68 [54; 87]	90.0 [78.0; 105.0]	56.5 [44.0; 64.5]	77.0 [64.0; 89.5]	68.0 [56.0; 88.0]	51.0 [44.5; 67.0]	< 0.001
Mitral *E'* wave, cm/s	10 [7.5; 13.6]	14.9 [13.0; 18.0]	8.9 [6.0; 10.9]	10.2 [8.3; 12.9]	8.7 [7.0; 11.4]	9.0 [7.0; 12.0]	< 0.001
E/E' ratio	6.8 [5.3; 9.3]	6.0 [4.6; 7.4]	6.6 [5.3; 9.4]	7.3 [5.5; 9.3]	8.4 [5.2; 11.1]	6.3 [4.3; 8.8]	0.003
Aortic VTI, cm	15.4 [12.8, 19]	16.0 [14.0; 18.6]	10.9 [8.7; 14.2]	19.6 [17.6; 23.8]	17.0 [13.9; 19.8]	13.2 [11.1; 15.7]	< 0.001
RV/LV EDA	0.6 [0.5; 0.8]	0.6 [0.5; 0.6]	0.6 [0.5; 0.7]	0.6 [0.5; 0.7]	0.8 [0.6; 0.9]	0.6 [0.5; 0.7]	< 0.001
ΔSVC, %	13.2 [6; 29.2]	12.5 [5.3; 22.0]	10.0 [5.4; 17.3]	10.8 [5.3; 17.8]	9.5 [3.1; 20.0]	39.4 [30.8; 54.0]	< 0.001

*Exact Fisher's test

**Only one patient received dobutamine

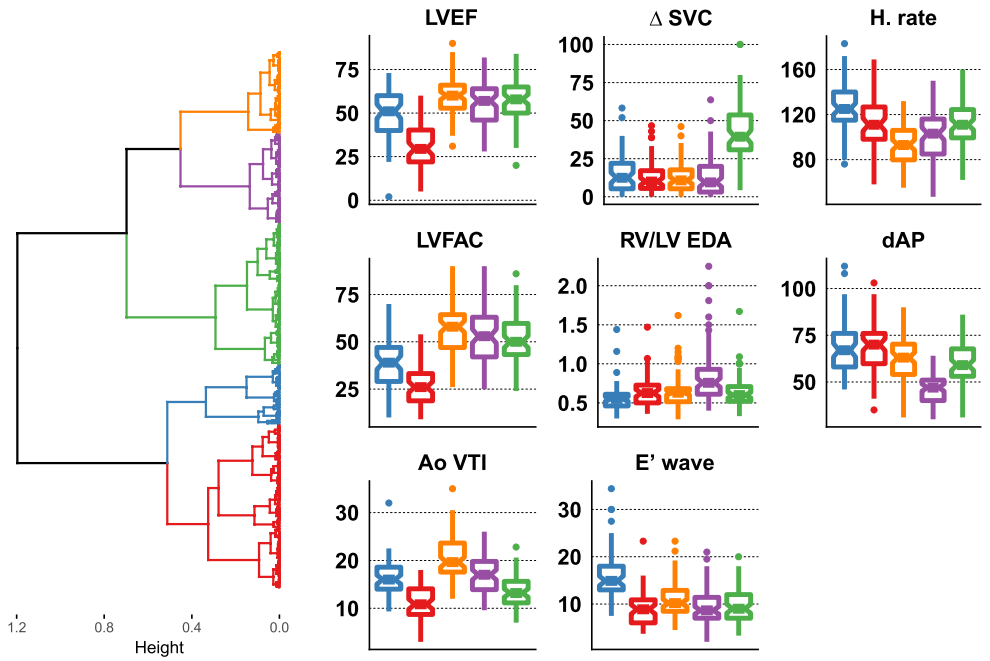


Fig. 1 Cardiovascular phenotypes. The left panel shows the dendrogram generated using the hierarchical clustering approach. The right panel shows the main hemodynamic parameters characterizing these cardiovascular phenotypes. LVEF left ventricular ejection fraction, LVFAC left ventricular fractional area change, Ao VTI aortic blood flow velocity time integral, ΔSVC superior vena cava collapsibility index, RV right ventricle, LV left ventricle, EDA end-diastolic area, H. rate heart rate, dAP diastolic arterial pressure

respectively, $p < 0.001$. ICU mortality was 21.3 [95% CI 13.0; 33.1], 50.0 [38.1; 61.9], 23.8 [16.0; 33.9], 42 [31.8; 52.8], and 38.6 [28.0; 50.3] % in clusters 1, 2, 3, 4, and 5, respectively ($p < 0.001$). Figure 2 and Table 3 report the distribution of parameters which characterize clusters as well as the respective importance of each of them in the partition process. Figure 3 reports the overall good performance of the three most important variables in each cluster, with a very high specificity but a quite low sensitivity.

Discussion

The clustering approach combining echocardiographic parameters (LVEF, LVFAC, aortic VTI, RV/LV EDA, ΔSVC, mitral *E* wave velocity, and *E*′ wave velocity) and clinical parameters (heart rate, blood pressure, type and dose of catecholamine) allowed us to characterize five distinct cardiovascular phenotypes, the hemodynamic profiles of which correspond to "well-resuscitated" patients (16.9%, cluster 1), patients with LV systolic dysfunction (17.7%, cluster 2), hyperkinetic profile (23.3%, cluster 3), RV failure (22.5%, cluster 4), and sustained hypovolemia (19.4%, cluster 5).

This approach in clustering without any a priori criteria was able to distinguish different phenotypes between all the expected alterations of the macrocirculation. In the LV systolic dysfunction phenotype (cluster 2), patients had a higher serum lactate level, a lower CI, and a higher dose of norepinephrine. While differences in lactate and CI probably reflect the severity of underlying septic cardiomyopathy, the higher dose of norepinephrine could have participated in the development of LV failure. It has been reported that in animal models alteration in LV intrinsic contraction is constant in sepsis [22] and that the level of LV afterload especially alters LVEF in this abnormal heart [23]. Accordingly, the increased dose of norepinephrine administered in this subset of patients could have unmasked, or even participated in, the observed LV systolic dysfunction by increasing afterload. Jardin et al. and Parker et al. reported higher systemic vascular resistance in patients with LV systolic dysfunction [2, 24]. Boissier et al. [25] recently reported a negative correlation between echocardiographic parameters of LV systolic function and those of LV afterload. Patients with this cardiovascular phenotype also failed to exhibit increased *E*/*E*′, which is widely considered as a surrogate of LV filling pressure [26]. The absence of elevation in LV filling pressure has been reported as a specific characteristic of this hemodynamic profile, not only when evaluated by the *E*/*E*′ but also when measured in the past using a pulmonary artery catheter [2, 24]. It was suggested to be related to an increase in LV compliance

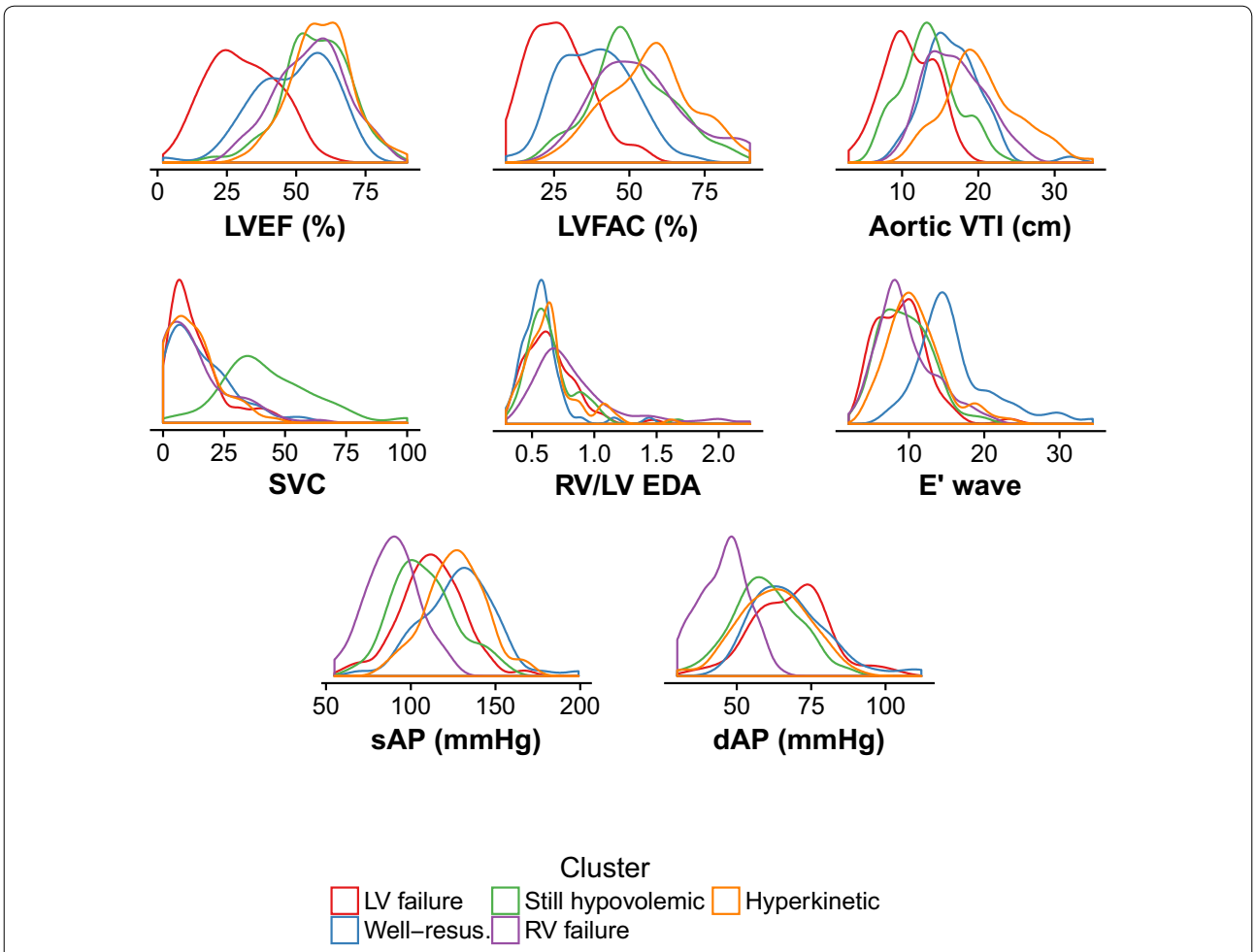


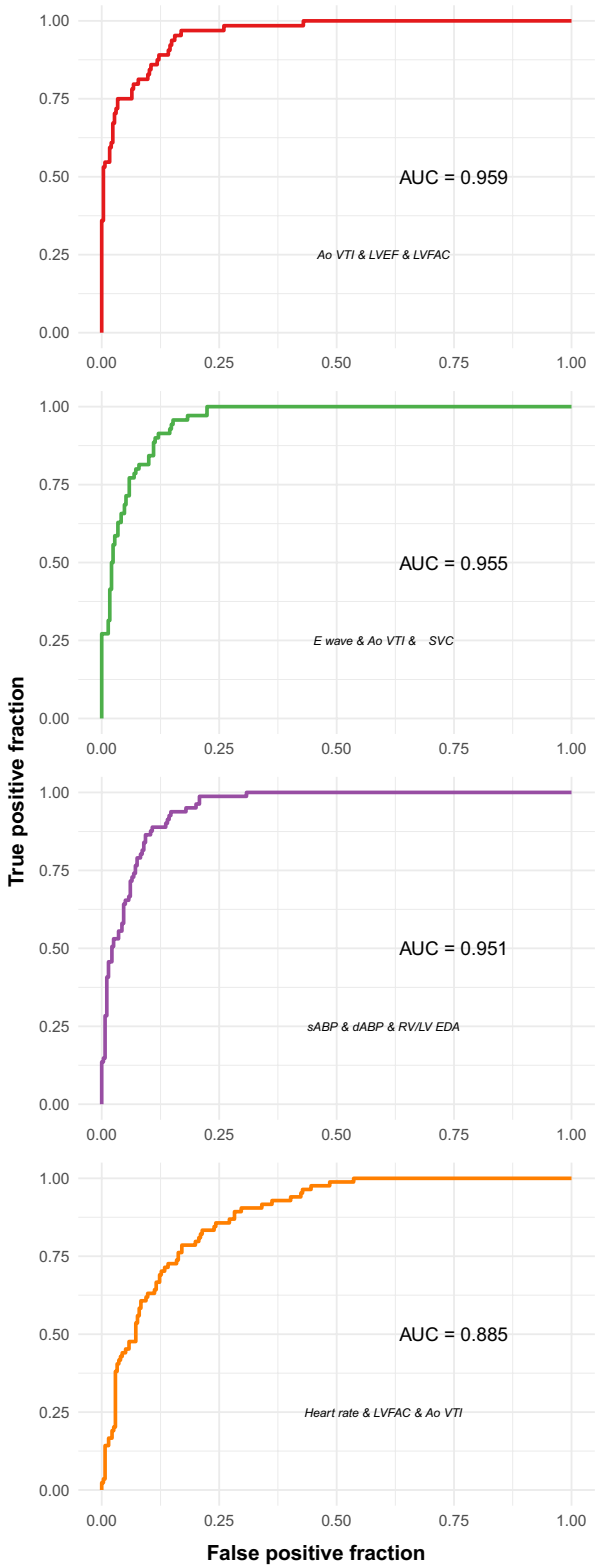
Fig. 2 Distribution of the factors contributing most in the clustering approach in the five cardiovascular phenotypes. LVEF left ventricular ejection fraction, LVFAC left ventricular fractional area change, Ao VTI aortic blood flow velocity time integral, ΔSVC superior vena cava collapsibility, RV right ventricle, LV left ventricle, EDA end-diastolic area, dAP diastolic arterial pressure, sAP systolic arterial pressure

Table 3 Variables that significantly contributed to the cluster

Variable	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5
LVEF (%)	–	**31/51 (4×10^{-30})**	59/51 (1×10^{-7})	56/51 (2×10^{-3})	57/51 (2×10^{-4})
LVFAC (%)	39/47 (10×10^{-5})	**26/47 (9×10^{-25})**	**57/47 (4×10^{-10})**	54/47 (2×10^{-5})	51/47 (1×10^{-2})
Aortic VTI (cm)	–	**11/16 (4×10^{-18})**	**20/16 (5×10^{-20})**	–	**14/16 (8×10^{-6})**
Mitral *E* wave (cm/s)	**92/71 (2×10^{-14})**	58/71 (1×10^{-6})	78/71 (2×10^{-3})	–	**55/71 (3×10^{-10})**
E' wave (cm/s)	**16/11 (5×10^{-22})**	9/11 (4×10^{-4})	–	10/11 (4×10^{-3})	10/11 (7×10^{-3})
RV/LV EDA	0.57/0.68 (8×10^{-4})	–	–	**0.85/0.68 (2×10^{-10})**	–
Δ SVC (%)	–	13/19 (2×10^{-3})	12/19 (8×10^{-5})	13/19 (2×10^{-3})	**43/19 (2×10^{-35})**
sBP (mmHg)	128/112 (4×10^{-9})	–	126/112 (3×10^{-10})	**89/112 (1×10^{-23})**	–
dBP (mmHg)	68/60 (9×10^{-7})	68/60 (5×10^{-7})	–	**45/60 (1×10^{-26})**	–
Heart rate (/min)	**127/108 (2×10^{-11})**	–	**93/108 (2×10^{-10})**	101/108 (9×10^{-3})	–
Norepinephrine infusion rate (mg/h)	–	3.8/2.6 (7×10^{-5})	1.6/2.6 (7×10^{-5})	3.1/2.6 (3×10^{-2})	–
Epinephrine infusion rate (mg/h)	–	0.3/0.1 (1×10^{-2})	–	0/0.1 (2×10^{-2})	–

Bold numbers show the three most important variables for each cluster. Values shown in each cell are mean in cluster/overall mean (*p* value)

LVEF left ventricular ejection fraction, *LVFAC* left ventricular fractional area change, *Ao VTI* aortic blood flow velocity time integral, *ΔSVC* superior vena cava collapsibility, *RV* right ventricle, *LV* left ventricle, *EDA* end-diastolic area, *dAP* diastolic arterial pressure, *sAP* systolic arterial pressure



LVEF <40% & Ao VTI <14cm & LVFAC <33%

LV failure	
n	35/64
Sensibility	54.7 [42.5;66.9]
Specificity	97.6 [95.9;99.4]
Pos. pred. value	83.3 [72.1;94.6]
Neg. pred. value	90.9 [87.7;94]

Ao VTI < 16 cm & E wave < 67 cm/s & SVC > 39 %

Hypovolemic	
n	18/70
Sensibility	25.7 [15.5;36]
Specificity	99.3 [98.4;100.3]
Pos. pred. value	90 [76.9;103.1]
Neg. pred. value	84.7 [80.9;88.5]

RV/LV EDA >0.8 & sABP <100mmHg & dABP <51mmHg

RV failure	
n	24/81
Sensibility	29.6 [19.7;39.6]
Specificity	98.9 [97.7;100.1]
Pos. pred. value	88.9 [77;100.7]
Neg. pred. value	82.9 [78.8;86.9]

Ao VTI >20cm & Heart rate <106bpm & LVFAC >58%

Hyperkinesia	
n	15/84
Sensibility	17.9 [9.7;26]
Specificity	98.2 [96.6;99.8]
Pos. pred. value	75 [56;94]
Neg. pred. value	79.7 [75.4;84]

Fig. 3 Performance of the combination of the three most important variables in the clustering approach for each cluster. The ROC curves on the left of the figure are drawn from a multivariable logistic regression with being in a cluster (binary variable yes/no) as the dependent variable and the three most important variables as independent variables. The areas under the curve and the three variables are listed on the plot. On the right of the figure are presented the diagnostic performance of the combination of the three variables for each cluster

due to sepsis [27]. Our clustering approach was also able to differentiate the "still hypovolemic" cardiovascular phenotype (cluster 5) from the "hyperkinetic" (cluster 3), both conditions being characterized by the presence of global LV hyperkinesia. Nevertheless, CI, aortic VTI (a surrogate of LV stroke volume), and CVP were lower in patients with persistent hypovolemia when compared to their counterparts, and ΔSVC was consistent with fluid responsiveness, as opposed to patients with a hyperkinetic hemodynamic profile. Patients who had a cardiovascular phenotype consistent with RV failure (cluster 4) were the only ones to exhibit a large increase in RV/LV EDA, which was recently considered to define RV failure [16] It is noteworthy that these patients had a higher proportion of PaO_2/FiO_2 level lower than 200 mmHg, suggesting that RV failure was potentially secondary to the development of ARDS-related septic shock. Finally, we failed to identify a cardiovascular phenotype corresponding to patients with isolated LV diastolic dysfunction, as previously reported [15]. In contrast, as indicated by the median E' maximal velocity, LV diastolic dysfunction was uniformly distributed in all phenotypes, with the exception of the well resuscitated patients (cluster 1).

Our approach may have potential interest for optimizing hemodynamic support using CCE after the very early resuscitation phase since personalized medicine has gained more and more importance [7]. A recent pilot study suggested that early vasopressor infusion could restrict fluid volume without detrimental effect on prognosis [9]. If our approach is able to better characterize patients who really need more fluids after the early phase, this could significantly change management and prognosis. While fluid overload is suggested to be detrimental [28], inappropriate use of vasopressors in still hypovolemic situations may lead to increase in tissue hypoperfusion and severe ischemia of vital organs [29]. The need for inotropic infusion in septic shock is still an issue of controversy. Indeed no study ever reported a relationship between LV systolic dysfunction and mortality and a beneficial effect of inotrope infusion. In a recent single-center randomized controlled trial, infusion of levosimendan did not modify prognosis but has deleterious cardiovascular effects [14]. However, the authors did not select their population at all on the basis of a pre-existing LV systolic dysfunction phenotype [14]. Our clustering approach, defining LV systolic dysfunction without a binary and simplistic threshold value of LVEF but by combining the usual echocardiographic and clinical hemodynamic variables as done in daily practice, could allow better characterization of these patients. How these patients could benefit from dobutamine infusion should be evaluated in the future. Finally, it is now well recognized that the right ventricle may fail in septic shock, especially when associated with ARDS, and that it may induce low flow state [30–32]. It was suggested that this profile may induce false positive pulse pressure variations [33, 34], a parameter frequently used to manage fluids. Accurately diagnosing RV failure could also help physicians to adequately optimize hemodynamic and respiratory support [30].

Our study suffers from limitations. First, even if one patient could only be statistically classified into one cardiovascular phenotype, interquartiles show a substantial between-cluster overlap for most studied parameters. This was expected since clusters were more defined by a specific association of parameters than by the presence of a single specific one. A soft clustering approach that addresses the overlapping issues might be of interest in future research [35]. Moreover, application of clustering in clinical practice is therefore not so obvious, even though we report in Fig. 3 and Table 3 the most valuable parameters that counted in the determination of each cluster and their value distribution. Last, the explained variance in the principal component analysis was quite low, reflecting the potential unmeasured factors we did not have to better describe these phenotypes. Second, we were unable to provide the exact timing of CCE following admission, which could alter our results, especially for the cluster 5 "still hypovolemic". However, we reported that these patients did not receive less fluid than the others before CCE performance, and even more, which may suggest a particular profile of capillary linkage. Third, we did not repeat the hemodynamic evaluation by CCE, as we only evaluated our cohort in the first 12 h after initial resuscitation of septic shock patients. It is of interest to assess in future studies whether the transition from one cardiovascular phenotype to another during the first 2–3 days could alter outcome, and whether it is related to spontaneous progression or induced by therapy. Fourth, variabilities of echo parameters were not calculated in the present cohort. However, the intraobserver and interobserver reproducibility of SVC collapsibility index were calculated as good to excellent in the Hemopred study [13]. The same authors, using the same route (TEE), in the same population (septic shock) previously reported interobserver variability of AoVTI, RV/LV EDA, LV volumes, and areas [10] which were below 10–11%. Fifth, we decided not to include in the analysis the 50 patients with a history of chronic heart failure. Indeed, we did not have any characterization of this failure; in particular, we did not know whether it was systolic, diastolic, valvular, injuring the right ventricle, and even the treatment. Finally, all CCE evaluations were performed by highly trained intensivists, which limits the external validity of our results, even though patients came from 12 different

ICUs and we reported in the past that the learning curve of TEE hemodynamic evaluation was steep and skills quickly achieved [36].

In conclusion, using a clustering approach in a large cohort of patients with septic shock evaluated early by CCE, we identified five distinct cardiovascular phenotypes which could help physicians to individualize the hemodynamic support. How this better characterization could change management and prognosis should be evaluated in the future.

Electronic supplementary material
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Author's contribution
GG, PV, AA and AVB designed the study and drafted the manuscript. PV, AA, ALF, CC, SS, XR and AVB collected the data. GG conducted the statistical analysis. AA, ALF, CC, SS and XR carefully revised the manuscript.

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Compliance with ethical standards

Conflicts of interest
GG, PV, AU, ALF, CC, SS, XR declared no conflict of interest. AVB has received grant from GSK for conducting clinical research and is a member of the scientific advisory board.

Ethical approval
Both cohorts (Hemosepsis and Hemopred) received Limoges ethics committee approval.

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